

# PATENT COOPERATION TREATY

WIPO

From the  
INTERNATIONAL SEARCHING AUTHORITY

to:  
**OGILVY RENAULT**  
1600 - 1981 McGill College Avenue  
MONTREAL, Quebec  
Canada, H3A 3C1

4/8

**PCT**  
REC'D 26 MAY 2005  
PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing 16 May 2005 (16-05-2005)  
(day/month/year)

Applicant's or agent's file reference  
8426-1854PCT

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.

**PCT/CA2005/000084**

International filing date (day/month/year)

25 January 2005 (25-01-2005)

Priority date (day/month/year)

27 January 2004 (27-01-2004)

International Patent Classification (IPC) or both national classification and IPC  
IPC 7 C07C 317/46

Applicant  
**MERCK FROSST CANADA & CO. ET AL**

1. This opinion contains indications relating to the following items :

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Box No. I    | Basis of the opinion  |
| <input checked="" type="checkbox"/> Box No. II   | Priority  |
| <input checked="" type="checkbox"/> Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/> Box No. IV              | Lack of unity of invention  |
| <input checked="" type="checkbox"/> Box No. V    | Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement. |
| <input type="checkbox"/> Box No. VI              | Certain documents cited   |
| <input checked="" type="checkbox"/> Box No. VII  | Certain defects in the international application  |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application   |

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA  
Canadian Intellectual Property Office  
Place du Portage I, C114 - 1st Floor, Box PCT  
50 Victoria Street  
Gatineau, Quebec K1A 0C9

Authorized officer

May Ling Nung (819) 997-2939

Facsimile No: 001(819)953-2476

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. I      Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. II**

**Priority**

1. ☐ The following document has not yet been furnished :

☐ copy of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

It has not yet been possible to consider the validity of the priority claim because the Authority does not have in its possession a copy of the earlier application on which priority has been claimed. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.  
PCT/CA2005/000084

**Box No. III**      **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of :

☐ the entire international application

☒ claim Nos. 6 -17

because:

☒ the said international application, or the said claim Nos. 6-17

relate to the following subject matter which does not require an international preliminary examination (*specify*) :

Although claims 6-17 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*) :

☐ the claims, or said claim Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos. \_\_\_\_\_

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form                      ☐ has not been furnished

☐ does not comply with the standard

the computer readable form      ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. V** Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**1. Statement**

Novelty (N)	Claims	1-19	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-19	NO
Industrial applicability (IA)	Claims	1-5, 18, 19	YES
	Claims		NO

**2. Citations and explanations :**

Reference is made to the following document:

D1 WO 01/45703  
D2 WO 03/103602

The present application refers to compounds of the general formula (I), a method of treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent, a method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1. Furthermore, independent claims 18 and 19 refer to pharmaceutical compositions comprising a compound of claim 1, aspirin and a carrier, and a compound of claim 1 and a carrier, respectively.

**1. Novelty**

None of the available prior art documents disclose compounds falling within the scope of the present product claims, pharmaceutical compositions containing them and their uses. Consequently, claims 1-19 are considered to meet the requirement of Art. 33(2) PCT.

**2. Inventive Step**

D1 discloses nitrosated and nitrosylated COX-2 inhibitors represented by the formula (III), wherein R<sup>1</sup> is SO<sub>2</sub>CH<sub>3</sub> or SO<sub>2</sub>NH<sub>2</sub>; R<sup>2</sup> is a mono-, di- or tri- substituted phenyl; Y<sup>3</sup> is CH<sub>2</sub>OC(O)R<sup>6</sup>, wherein R<sup>6</sup> is a substituted phenyl, lower alkyl or OR<sup>8</sup>, wherein R<sup>8</sup> is H or R<sup>9</sup>, wherein R<sup>9</sup> is lower alkyl; X<sup>3</sup> is C(O)-U-D<sup>1</sup>, wherein U is oxygen and D<sup>1</sup> is D, wherein D is K, wherein K is alkyl group with a terminal -O-NO or -O-NO<sub>2</sub>, which share most of the structural features with the present compounds of formula (I) (see page 4, line 26 to page 5, line 8 and lines 23-29; page 45, line 10 to page 47, line 22; page 91, line 27 to page 92, line 3, page 93, lines 15-19 and lines 29-31, and examples 12 and 14).

D2 discloses a nitrosated and/or nitrosylated cyclooxygenase 2 selective inhibitor represented by the formula (V) which has two nitrate groups, composition containing the same and methods of treating inflammatory diseases (see page 19, the formula (V) and page 31, lines 17 and 32-36, claim 3).

The documents D1 and D2 are regarded as representing the closest prior art which describe novel nitrosated and nitrosylated cyclooxygenase-2 (COX-2) inhibitors and compositions containing them and their uses.

*Continued in Supplemental Box*

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted :

In claim 1, at line 24, the word "with" is repeated and at line 25, "aromatic" should read "aromatic" (Article 6 PCT).

In claims 6 and 8, page 34, lines 21 and 30, the word "of" after the word "treatment" is redundant (Article 6 PCT).

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in WO 03/103602 and WO 97/28120 is not mentioned in the description, nor are these documents identified therein.

In claims 14 to 16, the use of the term "about" causes ambiguity. This term has no limiting effect when used in connection with ranges and leads to a lack of clarity as to the scope of said claims (Article 6 PCT).

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

According to the application (see especially page 2, third paragraph of the description) the problem underlying the invention is the provision of novel nitrosated compounds for cyclooxygenase-2 selective inhibitors.

To solve the problem the applicant provides the compounds of the general formula I of the present application, which differ from the compounds of D1 in having two NO-donor group instead of one NO-donor groups. Since it is known from D1 and D2 that COX-2 inhibitor can be substituted with more than one NO and/or NO<sub>2</sub> group, the person skilled in the art would have added one more NO-donor group in order to provide alternative compounds with the same activity and improved gastrointestinal and cardiovascular safety profiles and use said compounds as anti-inflammatory agents. Furthermore, the use of COX-2 inhibitors in conjunction with other therapeutic agents such as aspirin for co-therapies is taught in both D1 and D2.

Claims 1-19 are therefore considered as not meeting the requirement of Art. 33(3) PCT.

**3. Industry Applicability**

On the basis of the uses provided in the description, claims 1-5, 18 and 19 are therefore considered as meeting the requirement of Article 33(4) PCT.

The subject matter of claims 6-17 is directed to a method of medical treatment of the human or animal body (Rule 39.1(iv)PCT). No unified criteria exist in the PCT Contracting States for the assessment of the industrial applicability of claims 6-17 (Article 33(4)PCT).



# PATENT COOPERATION TREATY

WIPO

From the  
INTERNATIONAL SEARCHING AUTHORITY

to:  
**OGILVY RENAULT**  
1600 - 1981 McGill College Avenue  
MONTREAL, Quebec  
Canada, H3A 3C1

4/8

**PCT**  
REC'D 26 MAY 2005  
WIPO

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference <b>8426-1854PCT</b>	Date of mailing (day/month/year) <b>16 May 2005 (16-05-2005)</b>
<b>FOR FURTHER ACTION</b> See paragraph 2 below	

International application No. <b>PCT/CA2005/000084</b>	International filing date (day/month/year) <b>25 January 2005 (25-01-2005)</b>	Priority date (day/month/year) <b>27 January 2004 (27-01-2004)</b>
---	---	---

International Patent Classification (IPC) or both national classification and IPC  
**IPC 7 C07C 317/46**

**Applicant**  
**MERCK FROSST CANADA & CO. ET AL**

1. This opinion contains indications relating to the following items :

- ☒ Box No. I      Basis of the opinion
- ☒ Box No. II      Priority
- ☒ Box No. III      Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV      Lack of unity of invention
- ☒ Box No. V      Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
- ☐ Box No. VI      Certain documents cited
- ☒ Box No. VII      Certain defects in the international application
- ☒ Box No. VIII      Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9	Authorized officer  <div style="text-align: right;">May Ling Nung (819) 997-2939</div>
Facsimile No: 001(819)953-2476	

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. I      Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. II**

**Priority**

1. ☐ The following document has not yet been furnished :

☐ copy of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rules 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

It has not yet been possible to consider the validity of the priority claim because the Authority does not have in its possession a copy of the earlier application on which priority has been claimed. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.  
PCT/CA2005/000084

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of :

☐ the entire international application

☒ claim Nos. 6 -17

because:

☒ the said international application, or the said claim Nos. 6-17

relate to the following subject matter which does not require an international preliminary examination (*specify*) :

Although claims 6-17 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*) :

☐ the claims, or said claim Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos. \_\_\_\_\_

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. V** Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**1. Statement**

Novelty (N)	Claims	<u>1-19</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	_____	YES
	Claims	<u>1-19</u>	NO
Industrial applicability (IA)	Claims	<u>1-5, 18, 19</u>	YES
	Claims	_____	NO

**2. Citations and explanations :**

Reference is made to the following document:

D1 WO 01/45703  
D2 WO 03/103602

The present application refers to compounds of the general formula (I), a method of treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent, a method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1. Furthermore, independent claims 18 and 19 refer to pharmaceutical compositions comprising a compound of claim 1, aspirin and a carrier, and a compound of claim 1 and a carrier, respectively.

**1. Novelty**

None of the available prior art documents disclose compounds falling within the scope of the present product claims, pharmaceutical compositions containing them and their uses. Consequently, claims 1-19 are considered to meet the requirement of Art. 33(2) PCT.

**2. Inventive Step**

D1 discloses nitrosated and nitrosylated COX-2 inhibitors represented by the formula (III), wherein  $R^1$  is  $SO_2CH_3$  or  $SO_2NH_2$ ;  $R^2$  is a mono-, di- or tri- substituted phenyl;  $Y^3$  is  $CH_2OC(O)R^6$ , wherein  $R^6$  is a substituted phenyl, lower alkyl or  $OR^8$ , wherein  $R^8$  is H or  $R^9$ , wherein  $R^9$  is lower alkyl;  $X^3$  is  $C(O)-U-D^1$ , wherein U is oxygen and  $D^1$  is D, wherein D is K, wherein K is alkyl group with a terminal -O-NO or -O-NO<sub>2</sub>, which share most of the structural features with the present compounds of formula (I) (see page 4, line 26 to page 5, line 8 and lines 23-29; page 45, line 10 to page 47, line 22; page 91, line 27 to page 92, line 3, page 93, lines 15-19 and lines 29-31, and examples 12 and 14).

D2 discloses a nitrosated and/or nitrosylated cyclooxygenase 2 selective inhibitor represented by the formula (V) which has two nitrate groups, composition containing the same and methods of treating inflammatory diseases (see page 19, the formula (V) and page 31, lines 17 and 32-36, claim 3).

The documents D1 and D2 are regarded as representing the closest prior art which describe novel nitrosated and nitrosylated cyclooxygenase-2 (COX-2) inhibitors and compositions containing them and their uses.

*Continued in Supplemental Box*

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted :

In claim 1, at line 24, the word "with" is repeated and at line 25, "aromatice" should read "aromatic" (Article 6 PCT).

In claims 6 and 8, page 34, lines 21 and 30, the word "of" after the word "treatment" is redundant (Article 6 PCT).

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000084

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in WO 03/103602 and WO 97/28120 is not mentioned in the description, nor are these documents identified therein.

In claims 14 to 16, the use of the term "about" causes ambiguity. This term has no limiting effect when used in connection with ranges and leads to a lack of clarity as to the scope of said claims (Article 6 PCT).

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

According to the application (see especially page 2, third paragraph of the description) the problem underlying the invention is the provision of novel nitrosated compounds for cyclooxygenase-2 selective inhibitors.

To solve the problem the applicant provides the compounds of the general formula I of the present application, which differ from the compounds of D1 in having two NO-donor group instead of one NO-donor groups. Since it is known from D1 and D2 that COX-2 inhibitor can be substituted with more than one NO and/or NO<sub>2</sub> group, the person skilled in the art would have added one more NO-donor group in order to provide alternative compounds with the same activity and improved gastrointestinal and cardiovascular safety profiles and use said compounds as anti-inflammatory agents. Furthermore, the use of COX-2 inhibitors in conjunction with other therapeutic agents such as aspirin for co-therapies is taught in both D1 and D2.

Claims 1-19 are therefore considered as not meeting the requirement of Art. 33(3) PCT.

**3. Industry Applicability**

On the basis of the uses provided in the description, claims 1-5, 18 and 19 are therefore considered as meeting the requirement of Article 33(4) PCT.

The subject matter of claims 6-17 is directed to a method of medical treatment of the human or animal body (Rule 39.1(iv)PCT). No unified criteria exist in the PCT Contracting States for the assessment of the industrial applicability of claims 6-17 (Article 33(4)PCT).